

Pediatric Inflammatory Bowel Disease

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Inflammatory bowel diseases (IBDs) are chronic, immune-mediated disorders that include Crohn's disease and ulcerative colitis. A pediatric onset of disease occurs in about 10% of all cases. Clinical presentation of IBD with rectal bleeding or perianal disease warrants direct referral for endoscopic evaluation. In the absence of red-flag symptoms, a combination of patient history and blood and fecal biomarkers can help to distinguish suspected IBD from other causes of abdominal pain or diarrhea. The therapeutic management of pediatric IBD has evolved by taking into account predictors of poor outcome, which justifies the upfront use of anti-tumor necrosis factor therapy for patients at high risk for complicated disease. In treating patients with IBD, biochemical or endoscopic remission, rather than clinical remission, is the therapeutic goal because intestinal inflammation often persists despite resolution of abdominal symptoms. Pediatric IBD comes with unique additional challenges, such as growth impairment, pubertal delay, the psychology of adolescence, and development of body image. Even after remission has been achieved, many patients with IBD continue to experience nonspecific symptoms like abdominal pain and fatigue. Transfer to adult care is a well-recognized risk for disease relapse, which highlights patient vulnerability and the need for a transition program that is continued by the adult-oriented IBD team. The general pediatrician is an invaluable link in integrating these challenges in the clinical care of patients with IBD and optimizing their outcomes. This state-of-the-art review aims to provide general pediatricians with an update on pediatric IBD to facilitate interactions with pediatric gastrointestinal specialists.

Inflammatory bowel diseases (IBDs) are chronic, immune-mediated disorders that primarily affect the gastrointestinal (GI) tract and are characterized by alternating periods of inflammation (flares) and remission. IBDs are multifactorial diseases that depend on the complex interplay between host genotype, environment, microbiome, and immune system.¹⁻⁵ The incidence of pediatric IBD (PIBD) has increased rapidly during the past decades, especially in countries where the incidence used to be low.⁶ On the basis of 2 large US claims databases, the prevalence of PIBD more than doubled from 33 per 100 000 population in 2007 to 77 in 2016.⁷

IBDs include 2 distinct phenotypes: Crohn's disease (CD) and ulcerative colitis (UC) (Fig 1). CD manifests in the entire GI tract and perianal region and is characterized by transmural inflammation, patchy disease activity, segments with inflammation alternating with normal areas (skipped lesions), and the presence of strictures and/or fistulas. Involvement limited to the ileocolonic region represents the most-common presenting phenotype. Although frequently absent, the presence of granulomas distinguishes CD from UC.⁸ UC is typically confined to the colon and is characterized by continuous inflammation of the rectum that extends proximally,

abstract

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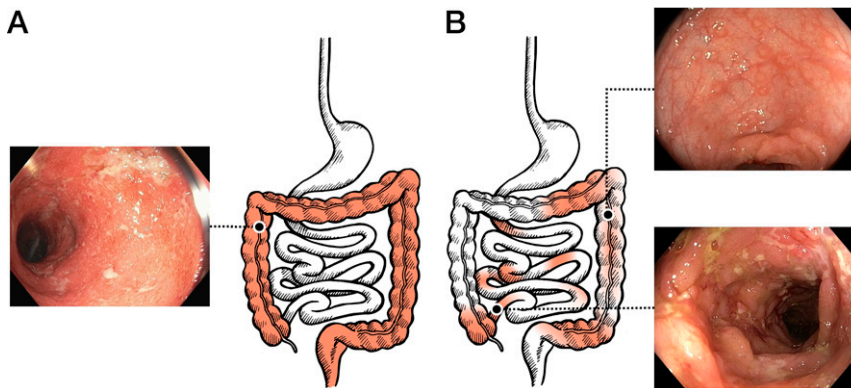


FIGURE 1

Pediatric IBD: common patterns of inflammation and endoscopic images. A: UC. Pancolitis. Diffuse inflammation with erythema, exudates, and loss of vascular pattern. B: CD. Skipped lesions in upper and lower GI tract. Deep longitudinal ulcers in the terminal ileum. Multiple aphthoid ulcers in the descending colon.

resulting in proctitis, left-sided colitis, or pancolitis,^{9,10} the latter being most common in children.¹¹ Backwash ileitis and upper GI tract involvement can occur but are uncommon in pediatric UC.¹²

In up to 10% of pediatric cases, the distinction between CD and UC is difficult. As the disease progresses, some of these IBD-unclassified cases later develop into either CD or UC.¹³ In a small proportion of children, IBD (especially UC) coexists with primary sclerosing cholangitis (PSC-IBD). The distribution of inflammation in the lower GI tract is so typical that PSC-IBD is often considered as a separate phenotype, with relatively mild intestinal symptoms, most active inflammation in the proximal colon, rectal sparing, and backwash ileitis. Children with PSC-IBD have a critical risk to develop colorectal cancer or cholangiocarcinoma.^{14,15}

Although still rare, the chances of identifying a monogenic disorder causing IBD-like intestinal inflammation are higher among children diagnosed with IBD before the age of 6 years (very

early onset IBD). These chances are the highest among children with an infantile disease onset, with estimations ranging between 13% and 41%.¹⁶ Monogenic causes of IBD comprise a growing list ranging from primary immunodeficiencies to intestinal epithelial cell defects, which often require a different therapeutic approach.¹⁷ Excellent reviews on this topic have recently been published elsewhere.^{16,18}

In this state-of-the-art review, we provide an overview of recent updates on PIBD by answering 5 questions that may come up in general practice:

1. how can I identify children with IBD among those with other causes of abdominal pain?;
2. how has the evidence-based treatment of pediatric IBD evolved?;
3. does childhood-onset IBD differ from adult-onset cases?;
4. can IBD be prevented in children at familial risk?; and
5. what is the role of the primary care provider in the comprehensive care team for children with IBD?

HOW CAN I IDENTIFY CHILDREN WITH IBD AMONG THOSE WITH OTHER CAUSES OF ABDOMINAL PAIN?

Early recognition of patients with suspected IBD and timely referral for endoscopic evaluation are important because diagnostic delay is associated with an increased risk of disease complications, such as stricturing or internal fistulizing complications and linear growth impairment at diagnosis.¹⁹ Patients with overt rectal bleeding or perianal disease (ie, abscesses, ulcers, or fistulae; but not skin tags or fissures), should be subjected to colonoscopy regardless of any biomarker result.²⁰ On the other hand, in children with milder symptoms, IBD may be more difficult to distinguish from other organic or functional disorders.²⁰

In a large, Swedish, population-based study, >25% of all children experienced recurrent functional abdominal pain before the age of 16 years, whereas <1% of this birth cohort was diagnosed with IBD during follow-up.²¹

For patients without the major red flags of overt rectal bleeding or perianal disease, a 3-tiered diagnostic workup based on symptoms, C-reactive protein, hemoglobin, and calprotectin is a highly accurate, noninvasive approach to investigation of possible IBD (Fig 2).²² Minor clinical red flags in children with chronic (ie, ≥ 4 weeks) abdominal pain, diarrhea, or both include having a first-degree relative with confirmed IBD, involuntary weight loss, and presence of extraintestinal manifestations.²²⁻²⁴ In some cases, extraintestinal organ involvement is more prominent than intestinal symptoms. The most-commonly involved organs are joints (arthropathy and arthritis), skin (including erythema nodosum and pyoderma gangrenosum), eyes

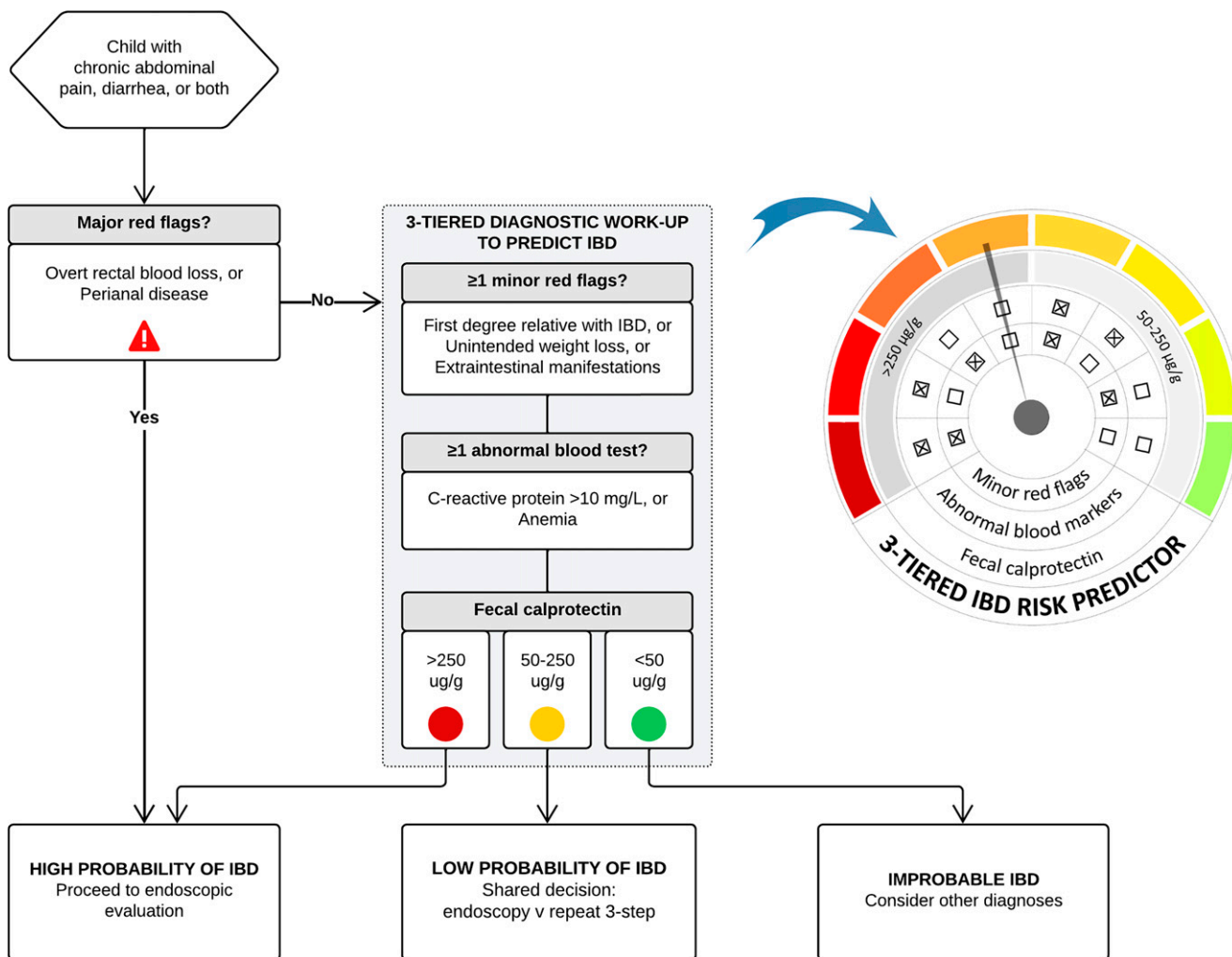


FIGURE 2

Decision tree: whether to scope for high suspicion of IBD. Use of this algorithm may help to decide whether your patient should proceed to endoscopy for verification of IBD, be followed for possible latent IBD to become visible, or be examined for any other causes of their complaints. The insert provides a visual aid to the interpretation of the 3-tiered diagnostic workup.

(including uveitis and episcleritis), and liver (including primary sclerosing cholangitis and autoimmune hepatitis).²⁵ Growth failure and delayed puberty are nonspecific, but can be the presenting symptoms in PIBD, particularly in CD.^{26,27}

Laboratory findings suggestive of IBD include anemia, increased inflammation markers, thrombocytosis, and low albumin. Complete absence of blood test abnormalities does not rule out IBD.²⁶

Fecal markers of inflammation correlate better with intestinal inflammation than blood markers. Calprotectin is a cytosolic protein complex with bacteriostatic properties primarily derived from neutrophils. If intestinal inflammation is present, the number of neutrophils in the intestinal lumen increases, resulting in an increased fecal calprotectin level.²⁸ When normal fecal calprotectin levels (<50 µg/g) are found, the diagnosis of IBD can be ruled out with confidence.²⁹ The probability of IBD increases in proportion to the

level of calprotectin. Referral for endoscopic evaluation is recommended when calprotectin levels exceed 250 µg/g and colon pathogens (including clostridium difficile) are not detected.³⁰⁻³²

Lactoferrin, another fecal marker, also correlates with the presence of neutrophil-mediated inflammation and is sometimes used as an alternative for fecal calprotectin. It has not been studied as widely as calprotectin, and whether it has any additional benefit is currently unknown.³³

HOW HAS THE EVIDENCE-BASED TREATMENT OF PEDIATRIC IBD EVOLVED?

Until recently, standard IBD treatment involved the initiation of conventional therapy with a step-up to biologicals if clinical remission (ie, resolution of symptoms) was not achieved. In patients with CD, remission induction consisted of either corticosteroids or exclusive enteral nutrition (EEN), irrespective of severity of disease or predictors of poor outcome.³⁴ EEN, which consists of a complete liquid formula-based diet for 6 to 8 weeks, is presumed to alter the immune response, reduce local inflammation, restore the functional epithelial and mucus barrier, and modify the microbiome.³⁵ Although both North American and European guidelines now recommend EEN as first-line treatment of pediatric CD patients with purely inflammatory disease, it is often underused in the United States. This is mostly because of practical concerns (unwillingness to disrupt normal life for a relatively long period, poor palatability).³⁵ Corticosteroids are equally effective in inducing remission, but may cause systemic side effects such as hypertension, hyperglycemia, and impaired bone health. Moreover, EEN has the benefit of improving the nutritional condition, which is often impaired at diagnosis.^{35,36}

In North America, methotrexate is the immunomodulator of choice to maintain remission.³⁷ Thiopurines (azathioprine or 6-mercaptopurine) used to be frequently prescribed, but many doctors now have reservations about the use of these drugs. Long-term use of thiopurines is associated with rare, but serious adverse outcomes, including lymphoma and nonmelanoma skin cancer.³⁷ In North America, thiopurines are now seldom used except for concomitant autoimmune liver disease.^{37,38} In Europe, where

thiopurines were always in favor, their use is now considered on an individual patient basis.³⁹

For pediatric UC, corticosteroids, aminosalicylates, or both are used for remission induction, and maintenance treatment primarily consists of aminosalicylate monotherapy (in Europe, frequently combined with a thiopurine).⁴⁰ EEN is currently not used in UC.

After induction therapy, most patients experience clinical improvement within 2 to 4 weeks.⁴¹ Although clinical remission traditionally has been the most important treatment goal, it has become clear that resolution of symptoms does not necessarily imply resolution of the underlying intestinal inflammation, thus putting the patients at risk for ongoing bowel damage and increased long-term morbidity.⁴² In contemporary IBD care, treatment goals have therefore become more ambitious. Symptomatic relief is considered a short-term target; clinical remission and normalization of fecal calprotectin and C-reactive protein are medium-term targets; and endoscopic and transmural healing, restoration of normal growth, normalized quality of life, and absence of disability are long-term targets. Histologic or molecular remission represent even deeper levels of remission, but are currently seen as controversial and unrealistic targets.⁴¹⁻⁴⁵

CD patients with predictors of poor outcome at disease onset (ie, panenteric disease, deep colonic ulcers, perianal fistula, stricturing and/or penetrating disease) are selected for upfront biological therapy (possibly combined with other treatments such as surgery) to achieve the treatment goals in a timely fashion.^{39,46,47} Upfront anti-

tumor necrosis factor (TNF) therapy should also be considered in case of severe growth delay. An early step-up to anti-TNF therapy is advised in all patients if the short- and medium-term treatment targets have not been reached 12 weeks after induction therapy was started.³⁹ Because thiopurines are generally not used in North America, a step-up to anti-TNF is more common in this region.⁴⁸

Kugathasan et al constructed and validated a prediction model on the basis of clinical, serological, and genetic markers that identify CD patients at high risk for disease complications who are likely to benefit from early anti-TNF therapy.⁴⁹ Adult studies suggest that early introduction of biologicals in UC could also be beneficial.⁵⁰ For UC patients, pediatric gastroenterologists and primary care providers alike can quickly calculate the Pediatric Ulcerative Colitis Activity Index, which is based on only a few key components in the patient history and provides a validated marker of current disease severity.⁵¹⁻⁵³

Therapeutic drug monitoring (TDM) has significantly refined the approach to biological agents because it makes provision for dose optimization, long-term efficacy, and minimization of adverse drug effects.⁵⁴ TDM consists of determining medication trough levels (serum levels right before the next intravenous or subcutaneous administration) to tailor the drug dose, the administration interval, or both to an individual's pharmacokinetics. Target trough levels are now well established for anti-TNF agents, but have not yet been sufficiently crystallized for the newer biologicals vedolizumab and ustekinumab.³⁹ An overview of the characteristics of the biologicals used in the treatment of PIBD can be found in Table 1.

TABLE 1 Biologic Agents for the Treatment of Pediatric IBD

Mechanism of Action	Generic Name	Route of Administration	Use
Anti-TNF	Infliximab	IV	<p>CD:</p> <ul style="list-style-type: none"> • Upfront in patients with predictors of poor outcome and/or severe growth delay • Step-up in case of nonresponse to conventional induction (EEN, steroids) or maintenance therapy (methotrexate, thiopurines)³⁸ <p>UC:</p> <ul style="list-style-type: none"> • Nonresponse or loss of response to conventional induction or maintenance therapy (aminosalicylates monotherapy or combination therapy with a thiopurine) • Steroid-dependent UC⁶⁴
	Adalimumab	SC	<p>CD:</p> <ul style="list-style-type: none"> • Upfront in patients with predictors of poor outcome and/or severe growth delay • Step-up in case of nonresponse to conventional induction or maintenance therapy³⁸ <p>UC:</p> <ul style="list-style-type: none"> • Loss of response to infliximab • Infliximab intolerance⁶⁴
	Golimumab ^a	SC	<p>UC:</p> <ul style="list-style-type: none"> • Loss of response to conventional maintenance therapy⁶⁴
	Vedolizumab ^a	IV	<p>CD and UC:</p> <ul style="list-style-type: none"> • Anti-TNF failure (nonresponse or loss of response)^{38,64}
Anti-integrin ($\alpha 4\beta 7$ integrin heterodimer)	Ustekinumab ^a	Single IV-loading dose, then SC maintenance doses	<p>CD:</p> <ul style="list-style-type: none"> • Anti-TNF failure (nonresponse or loss of response)³⁸

IL, interleukin; IV, intravenous; SC, subcutaneous.

^a No US Food and Drug Administration-approved labeling for use in children.

Two novel treatment strategies deserve special mention because of the attention they are receiving in the popular press, even though neither of these 2 are currently considered standard of care for PIBD. The first topic under study is whether the efficacy of EEN in CD may also be attained with an exclusion diet free from processed foods, which could overcome the limited palatability of liquid formula.⁵⁵ Several such diets are currently being studied, including the Crohn's Disease Exclusion Diet and CD Treatment-with-Eating Diet.⁵⁶⁻⁵⁸ The second innovative modality pertains to fecal microbiota transplantation (FMT), which aims to directly restore a dysbiotic microbiome and has demonstrated efficacy in adult patients with UC.^{59,60} Studies on its efficacy in children with UC and CD are currently ongoing.^{61,62} A recently published report described that children participating in such

trials and their parents consider FMT therapy from anonymous, screened donors acceptable and tolerable.⁶³

DOES CHILDHOOD-ONSET IBD DIFFER FROM ADULT-ONSET CASES?

Several studies have shown that patients who develop IBD during childhood are at higher risk for a more severe disease course and intestinal complications compared with cases with adult-onset.⁶⁵⁻⁶⁷ Part of this effect may be attributed to a longer lifetime risk, which provides more time to accrue cumulative inflammatory damage. However, childhood onset of disease may also identify those individuals who have the highest susceptibility for developing IBD and the factors that mediate this susceptibility may also contribute to more active and extensive disease.^{65,67} Compared with the general population, there is a threefold increase in the all-cause mortality risk of children with IBD

or adults with childhood-onset IBD.¹⁴ Part of this can be explained by the fact that children with IBD have an increased risk of cancer, especially GI cancer, although the absolute cancer risks are small.⁶⁸ Overall, extraintestinal manifestations at diagnosis are more common in children, with less involvement of joints.⁶⁹

PIBD often interferes with growth and development. Growth impairment can manifest as either weight loss/reduced weight gain or impaired height.⁷⁰ In a retrospective study of 436 PIBD patients, males with IBD had a significantly (but less than an inch) lower mean height at the beginning of adulthood compared with matched controls.⁷¹ Adolescents with IBD often continue to grow after expected growth plate closure, allowing for some additional catch-up growth during early adulthood.⁷² Pubertal delay is most common among females with CD

and timely referral (ie, as soon as pubertal delay is observed) to an endocrinologist is indicated for optimal management.^{27,73}

A particular challenge arises when children with IBD transition to adult care. This transition is not just a change from the children's hospital to the adult care clinic. The period between adolescence and full adulthood, called emerging adulthood, is often unstable because it is accompanied by many life events; complex changes on personal, social, emotional, neuroanatomical, and developmental levels; and declining levels of parental involvement.⁷⁴ An IBD diagnosis in a child is shared within a family: parents will not only help the patient to adhere to medication and to monitor disease activity, but will also serve as a knowledge base of previously received medical information and as a source of comfort and support during disease flares. Not uncommonly, parents prove to be more outspoken advocates for the patient's interests at the hospital or at school than the child. In IBD, emerging adulthood can be delayed and is associated with an increased risk of disease progression and complications, decreased treatment adherence, and higher health care costs.⁷⁵ Structured transitional care programs can help to address some of these challenges. In a meta-analysis that included adolescents with chronic inflammatory systemic diseases, the use of these programs resulted in significantly fewer hospital admissions during the first 2 years after transition and reduced surgery rates.⁷⁶

Finally, it deserves mention that the therapeutic arsenal for pediatric gastroenterologists is more restricted when compared with adult-care providers. Novel drugs undergo testing in the adult patient population, which often gives rise to

long lag times between a drug's first approval for adults and the pediatric population. For example, infliximab was approved for use in children with CD 8 years after its original approval in adults, whereas vedolizumab and ustekinumab have currently not been approved for children.⁷⁷⁻⁷⁹ As a result of this, many children are treated off-label, and pediatric data on dosing and safety are often lacking. The PIBD Network has published consensus statements to guide the design of pediatric clinical drug trials that could help to reduce the lag time.⁸⁰

CAN IBD BE PREVENTED IN CHILDREN AT FAMILIAL RISK?

Having a first-degree relative with IBD is the strongest known risk factor for developing IBD.⁸¹ Whether patients at increased familial risk could benefit from preventive strategies remains a challenge that defies 1 simple answer. Among the complex diseases, IBDs have been particularly well investigated by genome wide association studies. Combined genome wide association studies data from >25 000 patients have revealed >200 loci that increase the risk for either CD, UC, or (for the majority of loci) both.^{1,82,83} The candidate genes that map to these loci are involved in a diverse array of cellular functions, including the response to cellular stress, epithelial barrier integrity, and the innate immune response to bacterial molecules.⁸⁴ This extensive body of research suggests that IBD pathogenesis may originate from dysfunction in 1 of a great many interconnected and codependent molecular pathways that operate in conjunction to maintain immune homeostasis in the intestinal tract.⁸⁵ Because different molecular pathways undoubtedly vary in their sensitivity to perturbation by a particular environmental stressor, this conceptual view of IBD

pathogenesis may one day lead to a personalized IBD prevention advice that is tailored to a child's particular genetic susceptibility. At the current time, environmental risk factors associated with the development of IBD have only been identified at the population-level. Because these data have been derived predominantly from retrospective analyses, there is an inherent risk of recall bias and the possibility of reverse causation.² Associations have been described for several environmental factors, and some of these exert their effects during (early) childhood. In a recent summary of 53 meta-analyses on 71 environmental factors, smoking, urban living conditions, cesarean delivery, appendectomy, tonsillectomy, the use of antibiotics or oral contraceptives, lactose maldigestion, and vitamin D deficiency were all associated with an increased risk of CD. For UC urban living conditions, use of oral contraceptives and vitamin D deficiency were positive associations.² Conversely, breastfeeding, bed-sharing, high levels of vitamin D, and proximity to pets or farm animals were found to have protective effects on the development of IBD. Interestingly, smoking and appendectomy were risk factors for CD, but protective factors for UC.²

Of all environmental exposures, dietary habits are among the factors that may be most directly amenable to preventive modification. The risk of IBD increases with higher consumption of meat, sugar, and ultraprocessed foods,^{2,86,87} whereas high fiber, fruit, or vegetable intake are protective.² Animal studies and a limited number of studies in humans have shown that food additives, including artificial emulsifiers and sweeteners, can negatively affect gut microbiota composition and function.⁸⁸ Prospective studies that test

whether changes in diet can prevent IBD in subjects at risk are currently ongoing.^{89,90} Although a rigorous departure from a family's established dietary routine is notoriously hard to accomplish, an IBD diagnosis in a child should prompt a conversation on the importance of a healthy diet that may benefit the entire family, including yet unaffected siblings. Nutritionists with affinity for IBD care can be helpful partners in further substantiating this message.

Many of the environmental and dietary factors that associate with increased or reduced IBD risk are known to affect the intestinal microbiome. Consequently, changes to the composition of the microbiome may be the overarching mechanism via which these factors mediate their effect on IBD.^{91,92} In this light, approaches aimed at restoring a dysbiotic microbiome have been heralded as promising new avenues in the treatment of IBD. Although this has been an area of intense scientific investigation over the last few years, these endeavors have yet to culminate into clear, evidence-based recommendations. FMT appears more promising for UC than for CD,⁹³ but durability and consistency of therapeutic benefit remain contentious.^{91,92,94} The use of probiotics or prebiotics is not recommended in pediatric or adult IBD patients on the basis of the currently available data.^{95,96} Manipulation of the intestinal microbiome to avoid IBD in children

at risk should at this time not be advised outside the research setting.

WHAT IS THE ROLE OF THE PRIMARY CARE PROVIDER IN THE COMPREHENSIVE CARE TEAM FOR CHILDREN WITH IBD?

Caring for children with IBD requires meticulous health care management organized in a multidisciplinary team: a primary care provider, pediatric gastroenterologist, dietician, physiotherapist, and psychosocial support team.⁹⁷ The primary care provider may be confronted with inflammatory pathology that is located outside the gut. The pathogenesis of these extraintestinal manifestations is either dependent on translocation of immune responses from the intestine or is an independent inflammatory event that shares a common genetic predisposition.⁹⁸ It is a common misconception that extraintestinal manifestations ameliorate once the intestinal inflammation has been treated successfully. Although this may be true for erythema nodosum, oral aphthous ulcers, and episcleritis, anterior uveitis, ankylosing spondylitis, and primary sclerosing cholangitis appear to follow an independent disease course.⁹⁹

Fatigue may continue to affect a child's quality of life despite disease remission. It is often reported as one of the most severe and distressing symptoms.¹⁰⁰ Table 2 gives an overview of predictors of IBD-associated fatigue and

underlines its multifactorial treatment approach. Organic targets include treatment escalation to achieve a deeper level of healing, supplementation of iron and other micronutrients, and physical training.¹⁰¹ Given the negative impact of excessive use of electronic media devices on children's sleep, there is a need to screen for these bedtime activities.¹⁰²

A meta-analysis on the prevalence of anxiety and depression in PIBD showed that ~1 in 3 children had symptoms of anxiety, depression, or both, but only a fraction of them had an anxiety or depressive disorder.¹⁰³ The latter category of children is likely to benefit from a psychological intervention such as cognitive behavioral therapy. A significant proportion of PIBD patients receive repeated infusions of biologicals to induce and maintain remission, necessitating frequent intravenous placement. Topical anesthetics will control their pain but have no effect on needle anxiety. Children with a high degree of procedural fear are more likely to accumulate memories about more pain than they actually experienced. As a consequence, they develop anticipatory anxiety, which may culminate in posttraumatic stress. To mitigate medical trauma, distracting activities can be used, such as bubble blowing, puppets, imitation play, games, books, guided imagery, virtual reality, and hypnosis.¹⁰⁴

TABLE 2 Predictors of IBD-Associated Fatigue

Predictor of Fatigue	Worsens Fatigue	Improves Fatigue
Disease activity ¹⁰⁰	Active IBD (impaired physical well-being, disturbed sleep)	Endoscopic remission
Medication ¹⁰¹	Corticosteroids or anti-TNF agents	Successful antiinflammatory management
Hematologic factors ¹⁰¹	Anemia (iron deficiency, vitamin B ₁₂ deficiency, folate deficiency, anemia of chronic inflammation)	Suppletion of deficient nutrients
Family support ¹⁰⁰	Family disfunction	Maternal positive affect
Psychological factors ^{100,101}	Depression and anxiety	Cognitive behavioral therapy
Physical activity ^{115,116}	Impairment in motor function, decreased physical activity	Endurance training

Children with IBD may consult the primary care provider because of adverse drug effects, with increased susceptibility for infections being the most common.^{105,106} In a large, Swedish cohort study, the adjusted hazard ratio for serious infections (ie, resulting in hospitalization) was 9.5 (95% confidence interval 8.5–10.5) for PIBD patients compared with matched individuals from the general population.¹⁰⁷ Discontinuation of immunosuppressants is sometimes needed to speed up recovery.¹⁰⁶

Vaccine-preventable infections can have a severe course in children with IBD. Ideally, each child should have their vaccination status optimized before starting immunosuppressant therapy. Live-virus vaccines are contraindicated when high prednisolone doses (≥ 20 mg per day or for 2 weeks or more), thiopurines, methotrexate, or biological therapy are used. Live vaccines include measles, mumps, rubella; varicella-zoster virus; yellow fever; and the live attenuated oral influenza and oral typhoid vaccine. Annual influenza vaccination is indicated for all patients.¹⁰⁸

COVID-19 is a mild disease in most PIBD patients. However, those with severe active IBD, moderate to severe malnutrition, or high-dosed systemic corticosteroids have an increased risk for severe disease (ie, requiring admission to an ICU).¹⁰⁹ The international organization for the study of IBD recommends that all patients with IBD should be vaccinated against SARS-CoV-2.¹¹⁰ A study in children and young adults with IBD receiving infliximab or vedolizumab showed a significantly lower and less-durable antibody response to natural infection compared with adult non-IBD patients. Immunization did induce a strong antibody response, highlighting the importance of vaccinating these patients.¹¹¹

Another topic of concern is the risk of treatment-related malignancy. As mentioned previously, the risk of lymphoma has made a majority of North American pediatricians distance themselves from thiopurines, whereas, in Europe, the choice for either a thiopurine or methotrexate is considered on an individual patient basis.^{37,39} In a prospective cohort study, 5766 PIBD patient were followed up for a total of >24 000 patient-years. Of the 15 patients who developed a malignancy, 5 had lymphomas, of which 4 were exposed to thiopurines at the time of diagnosis. The increased malignancy risk does not appear to persist when thiopurines have been discontinued for a year or longer.¹¹²

An association between lymphoma risk and anti-TNF therapy has been described in adults,¹¹³ but in a systematic review in children, anti-TNF therapy did not significantly increase the risk of lymphoma.¹¹⁴

CONCLUSIONS

In this review, we provide an update on PIBD for the primary care provider by answering five questions.

How Can I Identify Children With IBD Among Those With Other Causes of Abdominal Pain?

The probability of IBD is high in children with rectal bleeding or perianal disease. In children with nonspecific symptoms, the evaluation of blood and stool markers is the optimal test strategy to select children for endoscopy.

How Has the Evidence-Based Treatment of Pediatric IBD Evolved?

Endoscopic remission and transmural healing have become important treatment targets. CD patients with predictors of poor

outcome should get upfront biological therapy. Therapeutic drug monitoring helps to optimize the efficacy of biological therapy.

Does Childhood-Onset IBD Differ From Adult-Onset Cases?

PIBD is characterized by more extensive disease and more disease complications. Additional challenges in children include growth impairment and pubertal delay.

Can IBD be Prevented in Children at Familial Risk?

Finding ways to prevent IBD in children at familial risk is a subject of scientific interest. A personalized IBD prevention strategy based on a child's genetic profile may someday become reality.

What is the Role of the Primary Care Provider in the Comprehensive Care Team for Children With IBD?

The primary care provider should be vigilant for signs of fatigue, anxiety, depression, and adverse drug effects.

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ABBREVIATIONS

CD: Crohn's disease
EEN: exclusive enteral nutrition
FMT: fecal microbial transplantation
GI: gastrointestinal
IBD: inflammatory bowel disease
PIBD: pediatric inflammatory bowel disease
PSC-IBD: inflammatory bowel disease associated with primary sclerosing cholangitis
TDM: therapeutic drug monitoring
TNF: tumor necrosis factor
UC: ulcerative colitis

REFERENCES

- Noel DD, Marinella P, Mauro G, et al. Genetic variants assessing Crohn's disease pattern in pediatric inflammatory bowel disease patients by a clinical exome survey. [Published online ahead of print, December 22, 2021] *Bioinform Biol Insights*. 2021;15:11779322211055285 <https://doi.org/10.1177/11779322211055285>
- Piovani D, Danese S, Peyrin-Biroulet L, Nikolopoulos GK, Lytras T, Bonovas S. Environmental risk factors for inflammatory bowel diseases: an umbrella review of meta-analyses. *Gastroenterology*. 2019;157(3):647–659.e4
- Aldars-García L, Chaparro M, Gisbert JP. Systematic review: the gut microbiome and its potential clinical application in inflammatory bowel disease. *Microorganisms*. 2021;9(5):977
- Torun A, Hupalowska A, Trzonkowski P, Kierkus J, Pyrzynska B. Intestinal microbiota in common chronic inflammatory disorders affecting children. [Published online June 7, 2021] *Front Immunol*. 2021;12:642166 <https://doi.org/10.3389/fimmu.2021.642166>
- Guan Q. A comprehensive review and update on the pathogenesis of inflammatory bowel disease. [Published December 1, 2019] *J Immunol Res*. 2019;2019:7247238 <https://doi.org/10.1155/2019/7247238>
- Kuenzig ME, Fung SG, Marderfeld L, et al. InsightScope Pediatric IBD Epidemiology Group. Twenty-first century trends in the global epidemiology of pediatric-onset inflammatory bowel disease: systematic review. *Gastroenterology*. 2022;162(4):1147–1159.e4
- Ye Y, Manne S, Treem WR, Bennett D. Prevalence of inflammatory bowel disease in pediatric and adult populations: recent estimates from large national databases in the United States, 2007–2016. *Inflamm Bowel Dis*. 2020;26(4):619–625
- Bousvaros A, Antonioli DA, Colletti RB, et al. North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition; Colitis Foundation of America. Differentiating ulcerative colitis from Crohn disease in children and young adults: report of a working group of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the Crohn's and Colitis Foundation of America. *J Pediatr Gastroenterol Nutr*. 2007;44(5):653–674
- Bharadwaj S, Narula N, Tandon P, Yaghoobi M. Role of endoscopy in inflammatory bowel disease. *Gastroenterol Rep (Oxf)*. 2018;6(2):75–82
- Kresak J, Shen B, Liu X. Histology correlation with common endoscopic abnormalities. In: Bo Shen, eds. *Atlas of Endoscopy Imaging in Inflammatory Bowel Disease*. Elsevier: Academic Press. 2020:525–544
- Aziz DA, Moin M, Majeed A, Sadiq K, Biloo AG. Paediatric inflammatory bowel disease: clinical presentation and disease location. *Pak J Med Sci*. 2017;33(4):793–797
- Abuquteish D, Putra J. Upper gastrointestinal tract involvement of pediatric inflammatory bowel disease: a pathological review. *World J Gastroenterol*. 2019;25(16):1928–1935
- Ledder O, Sonnino M, Birimberg-Schwartz L, et al. Appraisal of the PIBD-classes criteria: a multicentre validation. *J Crohn's Colitis*. 2020;14(12):1672–1679
- Olén O, Askling J, Sachs MC, et al. Increased mortality of patients with childhood-onset inflammatory bowel diseases, compared with the general population. *Gastroenterology*. 2019;156(3):614–622
- Joose ME, Aardoom MA, Kerns P, et al. Paediatric IBD Porto group of ESPGHAN. Malignancy and mortality in paediatric-onset inflammatory bowel disease: a 3-year prospective, multinational study from the paediatric IBD Porto group of ESPGHAN. *Aliment Pharmacol Ther*. 2018;48(5):523–537
- Uhlíř HH, Charbit-Henrion F, Kotlarz D, et al. Paediatric IBD Porto group of ESPGHAN. Clinical genomics for the diagnosis of monogenic forms of inflammatory bowel disease: a position paper from the Paediatric IBD Porto Group of European Society of Paediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr*. 2021;72(3):456–473
- Kelsen JR, Sullivan KE, Rabizadeh S, et al. North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition position paper on the evaluation and management for patients with very early-onset inflammatory bowel disease. *J Pediatr Gastroenterol Nutr*. 2020;70(3):389–403
- Ouahed J, Spencer E, Kotlarz D, et al. Very early onset inflammatory bowel disease: a clinical approach with a focus on the role of genetics and underlying immune deficiencies. *Inflamm Bowel Dis*. 2020;26(6):820–842
- Ricciuto A, Mack DR, Huynh HQ, et al. Diagnostic delay is associated with complicated disease and growth impairment in paediatric Crohn's Disease. *J Crohn's Colitis*. 2021;15(3):419–431
- Franke M, Geiß A, Greiner P, et al. The role of endoscopy in pediatric gastrointestinal bleeding. *Endosc Int Open*. 2016;4(9):E1011–E1016
- Sjölund J, Uusijärvi A, Tornkvist NT, et al. Prevalence and progression of recurrent abdominal pain, from early childhood to adolescence. *Clin Gastroenterol Hepatol*. 2021;19(5):930–938.e8
- Van de Vijver E, Heida A, Ioannou S, et al. CACATU Consortium. Test strategies to predict inflammatory bowel disease among children with nonbloody diarrhea. *Pediatrics*. 2020;146(2):e20192235
- Heida A, Van de Vijver E, van Ravenzwaaij D, et al. CACATU Consortium. Predicting inflammatory bowel disease in children with abdominal pain and diarrhoea: calgranulin-C versus calprotectin stool tests. *Arch Dis Child*. 2018;103(6):565–571
- Fiorino G, Bonovas S, Gilardi D, et al. Validation of the red flags index for early diagnosis of Crohn's Disease: a prospective observational IG-IBD study among general practitioners. *J Crohn's Colitis*. 2020;14(12):1777–1779
- Jang HJ, Kang B, Choe BH. The difference in extraintestinal manifestations of inflammatory bowel disease for children and adults. *Transl Pediatr*. 2019;8(1):4–15
- Oliveira SB, Monteiro IM. Diagnosis and management of inflammatory bowel disease in children. *BMJ*. 2017;357:j2083
- Amaro F, Chiarelli F. Growth and puberty in children with inflammatory bowel diseases. *Biomedicine*. 2020;8(11):458
- Jukic A, Bakiri L, Wagner EF, Tilg H, Adolph TE. Calprotectin: from biomarker to biological function. *Gut*. 2021;70(10):1978–1988

29. Koninckx GR, Donat E, Benninga MA, et al. The use of fecal calprotectin testing in paediatric disorders: A position paper of the European Society for Paediatric Gastroenterology and Nutrition Gastroenterology Committee. *J Pediatr Gastroenterol Nutr*. 2021;72(4):617–640
30. Orfei M, Gasparetto M, Hensel KO, Zellweger F, Heuschkel RB, Zilbauer M. Guidance on the interpretation of faecal calprotectin levels in children. *PLoS One*. 2021;16(2):e0246091
31. Smalley W, Falck-Ytter C, Carrasco-Labra A, Wani S, Lytvyn L, Falck-Ytter Y. AGA clinical practice guidelines on the laboratory evaluation of functional diarrhea and diarrhea-predominant irritable bowel syndrome in adults (IBS-D). *Gastroenterology*. 2019;157(3):851–854
32. Degraeuwe PL, Beld MP, Ashorn M, et al. Faecal calprotectin in suspected paediatric inflammatory bowel disease. *J Pediatr Gastroenterol Nutr*. 2015;60(3):339–346
33. Vernia F, Viscido A, Di Ruscio M, Stefanelli G, Valvano M, Latella G. Fecal lactoferrin and other putative fecal biomarkers in Crohn's disease: do they still have a potential clinical role? *Digestion*. 2021;102(6):833–844
34. Ruemmele FM, Veres G, Kolho KL, et al. European Crohn's and Colitis Organisation; European Society of Pediatric Gastroenterology, Hepatology and Nutrition. Consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohn's disease. *J Crohn's Colitis*. 2014;8(10):1179–1207
35. Ashton JJ, Gavin J, Beattie RM. Exclusive enteral nutrition in Crohn's disease: evidence and practicalities. *Clin Nutr*. 2019;38(1):80–89
36. Yu Y, Chen KC, Chen J. Exclusive enteral nutrition versus corticosteroids for treatment of pediatric Crohn's disease: a meta-analysis. *World J Pediatr*. 2019;15(1):26–36
37. Mack DR, Benchimol EI, Critch J, et al. Canadian Association of Gastroenterology clinical practice guideline for the medical management of pediatric luminal Crohn's disease. *Gastroenterology*. 2019;157(2):320–348
38. Saubermann LJ, Deneau M, Falcone RA, et al. Hepatic issues and complications associated with inflammatory bowel disease: a clinical report from the NASPGHAN inflammatory bowel disease and hepatology committees. *J Pediatr Gastroenterol Nutr*. 2017;64(4):639–652
39. van Rheenen PF, Aloï M, Assa A, et al. The medical management of paediatric Crohn's disease: an ECCO-ESPGHAN guideline update. [Published online ahead of print October 7, 2020] *J Crohn's Colitis*. 2020;jjaa161 <https://doi.org/10.1093/ecco-jcc/jjaa161>
40. Turner D, Levine A, Escher JC, et al. European Crohn's and Colitis Organization; European Society for Paediatric Gastroenterology, Hepatology, and Nutrition. Management of pediatric ulcerative colitis: joint ECCO and ESPGHAN evidence-based consensus guidelines. *J Pediatr Gastroenterol Nutr*. 2012;55(3):340–361
41. Turner D, Ricciuto A, Lewis A, et al. International Organization for the Study of IBD. STRIDE-II: an update on the selecting therapeutic targets in inflammatory bowel disease (STRIDE) initiative of the International Organization for the Study of IBD (IOIBD): determining therapeutic goals for treat-to-target strategies in IBD. *Gastroenterology*. 2021;160(5):1570–1583
42. Berg DR, Colombel JF, Ungaro R. The role of early biologic therapy in inflammatory bowel disease. *Inflamm Bowel Dis*. 2019;25(12):1896–1905
43. Zilbauer M, Heuschkel R. Disease prognostic biomarkers in inflammatory bowel diseases—a reality check. *J Crohn's Colitis*. 2022;16(1):162–165
44. Yoon H, Jangi S, Dulai PS, et al. Incremental benefit of achieving endoscopic and histologic remission in patients with ulcerative colitis: a systematic review and meta-analysis. *Gastroenterology*. 2020;159(4):1262–1275.e7
45. Meserve J, Singh S. Pathologist, meet Picasso! Virtual chromoendoscopy for detecting histologic remission in ulcerative colitis. *Gastroenterology*. 2021;160(5):1469–1472
46. Kang B, Choe YH. Early biologic treatment in pediatric Crohn's disease: catching the therapeutic window of opportunity in early disease by treat-to-target. *Pediatr Gastroenterol Hepatol Nutr*. 2018;21(1):1–11
47. Agrawal M, Spencer EA, Colombel JF, Ungaro RC. Approach to the management of recently diagnosed inflammatory bowel disease patients: a user's guide for adult and pediatric gastroenterologists. *Gastroenterology*. 2021;161(1):47–65
48. Church PC, Hyams J, Ruemmele F, de Ridder L, Turner D, Griffiths AM. The continental divide: anti-TNF use in pediatric IBD is different in North America compared to other parts of the world. [Published online June 12, 2018] *Can J Gastroenterol Hepatol*. 2018;2018:3190548 <https://doi.org/10.1155/2018/3190548>
49. Kugathasan S, Denson LA, Walters TD, et al. Prediction of complicated disease course for children newly diagnosed with Crohn's disease: a multicentre inception cohort study. *Lancet*. 2017;389(10080):1710–1718
50. Yuan W, Marwaha JS, Rakowsky ST, et al. Trends in medical management of moderately to severely active ulcerative colitis: a nationwide retrospective analysis. [Published online ahead of print July 4, 2022] *Inflamm Bowel Dis*. 2022; [izac134](https://doi.org/10.1093/ibd/izac134) <https://doi.org/10.1093/ibd/izac134>
51. Turner D, Otley AR, Mack D, et al. Development, validation, and evaluation of a pediatric ulcerative colitis activity index: a prospective multicenter study. *Gastroenterology*. 2007;133(2):423–432
52. Turner D, Griffiths AM, Veerman G, et al. Endoscopic and clinical variables that predict sustained remission in children with ulcerative colitis treated with infliximab. *Clin Gastroenterol Hepatol*. 2013;11(11):1460–1465
53. Organisation ECsaC. Paediatric Ulcerative Colitis Activity Index (PUCAI). Available at: www.e-guide.ecco-ibd.eu/resources/calculator/paediatric-ulcerative-colitis-activity-index-puca. Accessed Aug 17, 2022
54. Kapoor A, Crowley E. Advances in therapeutic drug monitoring in biologic therapies for pediatric inflammatory bowel disease. [Published online May 26, 2021] *Front Pediatr*. 2021;9:661536 <https://doi.org/10.3389/fped.2021.661536>
55. Mckirdy S, Russell RK, Svolos V, et al. The impact of compliance during exclusive enteral nutrition on faecal calprotectin in children with Crohn disease.

- J Pediatr Gastroenterol Nutr.* 2022;74(6): 801–804
56. Levine A, Wine E, Assa A, et al. Crohn's disease exclusion diet plus partial enteral nutrition induces sustained remission in a randomized controlled trial. *Gastroenterology.* 2019;157(2): 440–450.e8
 57. Svolos V, Hansen R, Nichols B, et al. Treatment of active Crohn's disease with an ordinary food-based diet that replicates exclusive enteral nutrition. *Gastroenterology.* 2019;156(5):1354–1367.e6
 58. Verburgt CM, Ghiboub M, Benninga MA, de Jonge WJ, Van Limbergen JE. Nutritional therapy strategies in pediatric Crohn's disease. *Nutrients.* 2021;13(1): 212
 59. Fehily SR, Basnayake C, Wright EK, Kamm MA. Fecal microbiota transplantation therapy in Crohn's disease: systematic review. *J Gastroenterol Hepatol.* 2021;36(10):2672–2686
 60. Zhao HL, Chen SZ, Xu HM, et al. Efficacy and safety of fecal microbiota transplantation for treating patients with ulcerative colitis: a systematic review and meta-analysis. *J Dig Dis.* 2020;21(10): 534–548
 61. Pai N, Popov J. Protocol for a randomized, placebo-controlled pilot study for assessing feasibility and efficacy of faecal microbiota transplantation in a paediatric ulcerative colitis population: PediFETCh trial. *BMJ Open.* 2017; 7(8):e016698
 62. Pai N, Popov J, Hill L, Hartung E. Protocol for a double-blind, randomized, placebo-controlled pilot study for assessing the feasibility and efficacy of faecal microbiota transplant in a paediatric Crohn's disease population: PediCRaFT Trial. *BMJ Open.* 2019;9(11):e030120
 63. Popov J, Hartung E, Hill L, Chauhan U, Pai N. Pediatric patient and parent perceptions of fecal microbiota transplantation for the treatment of ulcerative colitis. *J Pediatr Gastroenterol Nutr.* 2021;73(6):684–688
 64. Turner D, Ruemmele FM, Orlanski-Meyer E, et al. Management of paediatric ulcerative colitis, part 1: ambulatory care—an evidence-based guideline from European Crohn's and Colitis Organization and European Society of Paediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr.* 2018;67(2): 257–291
 65. Pigneur B, Seksik P, Viola S, et al. Natural history of Crohn's disease: comparison between childhood- and adult-onset disease. *Inflamm Bowel Dis.* 2010;16(6): 953–961
 66. Jakobsen C, Bartek J Jr, Wewer V, et al. Differences in phenotype and disease course in adult and paediatric inflammatory bowel disease—a population-based study. *Aliment Pharmacol Ther.* 2011;34(10):1217–1224
 67. Herzog D, Fournier N, Buehr P, et al. Swiss IBD Cohort Study Group. Prevalence of intestinal complications in inflammatory bowel disease: a comparison between paediatric-onset and adult-onset patients. *Eur J Gastroenterol Hepatol.* 2017;29(8):926–931
 68. Olén O, Askling J, Sachs MC, et al. Childhood onset inflammatory bowel disease and risk of cancer: a Swedish nationwide cohort study 1964–2014. *BMJ.* 2017;358:j3951
 69. Greuter T, Bertoldo F, Rechner R, et al. Swiss IBD Cohort Study Group. Extraintestinal manifestations of pediatric inflammatory bowel disease: prevalence, presentation, and anti-TNF treatment. *J Pediatr Gastroenterol Nutr.* 2017;65(2): 200–206
 70. Wong K, Isaac DM, Wine E. Growth delay in inflammatory bowel diseases: significance, causes, and management. *Dig Dis Sci.* 2021;66(4):954–964
 71. Rinawi F, Assa A, Almagor T, Ziv-Baran T, Shamir R. Prevalence and predictors of growth impairment and short stature in pediatric-onset inflammatory bowel disease. *Digestion.* 2020;101(6):674–682
 72. Gupta N, Liu C, King E, et al. ImproveCareNow Network. Continued statural growth in older adolescents and young adults with Crohn's disease and ulcerative colitis beyond the time of expected growth plate closure. *Inflamm Bowel Dis.* 2020;26(12):1880–1889
 73. Kao KT, Denker M, Zacharin M, Wong SC. Pubertal abnormalities in adolescents with chronic disease. *Best Pract Res Clin Endocrinol Metab.* 2019;33(3):101275
 74. Wood D, Crapnell T, Lau L, et al. *Emerging Adulthood as a Critical Stage in the Life Course. Handbook of Life Course Health Development.* Cham: Springer; 2018
 75. Afzali A, Wahbeh G. Transition of pediatric to adult care in inflammatory bowel disease: Is it as easy as 1, 2, 3? *World J Gastroenterol.* 2017;23(20):3624–3631
 76. García-Rodríguez F, Raygoza-Cortez K, Moreno-Hernandez L, et al. Outcomes of transitional care programs on adolescent chronic inflammatory systemic diseases: systematic review and meta-analyses. [Published online February 17, 2022] *Pediatr Rheumatol Online J.* 2022;20(1):15 <https://doi.org/10.1186/s12969-022-00670-1>
 77. Turner D, Koletzko S, Griffiths AM, et al. Use of placebo in pediatric inflammatory bowel diseases: a position paper from ESPGHAN, ECCO, PIBDnet, and the Canadian Children IBD Network. *J Pediatr Gastroenterol Nutr.* 2016;62(1): 183–187
 78. Takeda Pharmaceuticals America, Inc. Highlights of prescribing information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125476s025s0301b1.pdf. Accessed April 28, 2022
 79. Janssen Biotech, Inc. STELARA (ustekinumab) injection, for subcutaneous or intravenous. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/7610441b1.pdf. Accessed April 28, 2022
 80. Turner D, Griffiths AM, Wilson D, et al. Designing clinical trials in paediatric inflammatory bowel diseases: a PIBDnet commentary. *Gut.* 2020;69(1):32–41
 81. Santos MPC, Gomes C, Torres J. Familial and ethnic risk in inflammatory bowel disease. *Ann Gastroenterol.* 2018;31(1): 14–23
 82. Jostins L, Ripke S, Weersma RK, et al. International IBD Genetics Consortium (IBDGC). Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. *Nature.* 2012;491(7422):119–124
 83. Liu JZ, van Sommeren S, Huang H, et al. International Multiple Sclerosis Genetics Consortium; International IBD Genetics Consortium. Association analyses identify 38 susceptibility loci for inflammatory bowel disease and highlight shared genetic risk across populations. *Nat Genet.* 2015;47(9):979–986

84. Peloquin JM, Goel G, Villablanca EJ, Xavier RJ. Mechanisms of pediatric inflammatory bowel disease. *Annu Rev Immunol.* 2016;34:31–64
85. Graham DB, Xavier RJ. Pathway paradigms revealed from the genetics of inflammatory bowel disease. *Nature.* 2020;578(7796):527–539
86. Khademi Z, Milajerdi A, Larijani B, Esmailzadeh A. Dietary intake of total carbohydrates, sugar and sugar-sweetened beverages, and risk of inflammatory bowel disease: a systematic review and meta-analysis of prospective cohort studies. [Published online October 1, 2021] *Front Nutr.* 2021;8:707795 <https://doi.org/10.3389/fnut.2021.707795>
87. Narula N, Wong ECL, Dehghan M, et al. Association of ultra-processed food intake with risk of inflammatory bowel disease: prospective cohort study. *BMJ.* 2021;374(1554):n1554
88. Raoul P, Cintoni M, Palombaro M, et al. Food additives, a key environmental factor in the development of IBD through gut dysbiosis. *Microorganisms.* 2022; 10(1):167
89. National Institutes of Health; U.S. National Library of Medicine; ClinicalTrials.gov. Prevention of inflammatory bowel diseases in persons at risk the PIONIR (preventing IBD onset in individuals at risk) Trial (PIONIR). Available at: <https://ClinicalTrials.gov/show/NCT05211518>. Accessed March 29, 2022
90. Limketkai BN, Hamideh M, Shah R, Sauk JS, Jaffe N. Dietary patterns and their association with symptoms activity in inflammatory bowel diseases. [Published online ahead of print January 29, 2022] *Inflamm Bowel Dis.* 2022;izab335 <https://doi.org/10.1093/ibd/izab335>
91. Plichta DR, Graham DB, Subramanian S, Xavier RJ. Therapeutic opportunities in inflammatory bowel disease: mechanistic dissection of host-microbiome relationships. *Cell.* 2019;178(5):1041–1056
92. Shan Y, Lee M, Chang EB. The gut microbiome and inflammatory bowel diseases. *Annu Rev Med.* 2022;73:455–468
93. Paramsothy S, Kamm MA, Kaakoush NO, et al. Multidonor intensive faecal microbiota transplantation for active ulcerative colitis: a randomised placebo-controlled trial. *Lancet.* 2017;389(10075):1218–1228
94. Chande N, Costello SP, Limketkai BN, et al. Alternative and complementary approaches for the treatment of inflammatory bowel disease: evidence from cochrane reviews. *Inflamm Bowel Dis.* 2020;26(6):843–851
95. Preidis GA, Weizman AV, Kashyap PC, Morgan RL. AGA technical review on the role of probiotics in the management of gastrointestinal disorders. *Gastroenterology.* 2020;159(2):708–738.e4
96. Serena G, Fasano A. Use of probiotics to prevent celiac disease and IBD in pediatrics. *Adv Exp Med Biol.* 2019;1125:69–81
97. DeFilippis EM, Sockolow R, Barfield E. Health care maintenance for the pediatric patient with inflammatory bowel disease. *Pediatrics.* 2016;138(3):e20151971
98. Hedin CRH, Vavricka SR, Stagg AJ, et al. The pathogenesis of extraintestinal manifestations: implications for IBD research, diagnosis, and therapy. *J Crohn's Colitis.* 2019;13(5):541–554
99. Rogler G, Singh A, Kavanaugh A, Rubin DT. Extraintestinal manifestations of inflammatory bowel disease: current concepts, treatment, and implications for disease management. *Gastroenterology.* 2021;161(4):1118–1132
100. Van de Vijver E, Van Gils A, Beckers L, Van Driessche Y, Moes ND, van Rheenen PF. Fatigue in children and adolescents with inflammatory bowel disease. *World J Gastroenterol.* 2019;25(5):632–643
101. Nocerino A, Nguyen A, Agrawal M, Mone A, Lakhani K, Swaminath A. Fatigue in inflammatory bowel diseases: etiologies and management. *Adv Ther.* 2020;37(1):97–112
102. Lund L, Sølvhøj IN, Danielsen D, Andersen S. Electronic media use and sleep in children and adolescents in western countries: a systematic review. *BMC Public Health.* 2021;21(1):1598
103. Stapersma L, van den Brink G, Szigethy EM, Escher JC, Utens EMWJ. Systematic review with meta-analysis: anxiety and depression in children and adolescents with inflammatory bowel disease. *Aliment Pharmacol Ther.* 2018;48(5):496–506
104. Krauss BS, Calligaris L, Green SM, Barbi E. Current concepts in management of pain in children in the emergency department. *Lancet.* 2016;387(10013):83–92
105. Dipasquale V, Romano C. Pharmacological treatments and infectious diseases in pediatric inflammatory bowel disease. *Expert Rev Gastroenterol Hepatol.* 2018;12(3):237–247
106. Kucharzik T, Ellul P, Greuter T, et al. ECCO guidelines on the prevention, diagnosis, and management of infections in inflammatory bowel disease. *J Crohn's Colitis.* 2021;15(6):879–913
107. Ludvigsson JF, Sachs MC, Järås J, Malmberg P, Olén O. Serious infections in pediatric inflammatory bowel disease 2002–2017—a nationwide cohort study. *J Pediatr.* 2021;238:66–73.e1
108. Ardura MI, Toussi SS, Siegel JD, Lu Y, Bousvaros A, Crandall W. NASPGHAN clinical report: surveillance, diagnosis, and prevention of infectious diseases in pediatric patients with inflammatory bowel disease receiving tumor necrosis factor- α inhibitors. *J Pediatr Gastroenterol Nutr.* 2016;63(1):130–155
109. Benchimol EI, Carroll MW, Geist R, et al. Crohn's and colitis Canada's 2021 impact of COVID-19 and inflammatory bowel disease in Canada: children and expectant mothers with inflammatory bowel disease. *J Can Assoc Gastroenterol.* 2021;4(Suppl 2):S27–S33
110. Siegel CA, Melmed GY, McGovern DP, et al. International Organization for the Study of Inflammatory Bowel Disease (IOIBD); International Organization for the Study of Inflammatory Bowel Diseases (IOIBD). SARS-CoV-2 vaccination for patients with inflammatory bowel diseases: recommendations from an international consensus meeting. *Gut.* 2021;70(4):635–640
111. Dailey J, Kozhaya L, Dogan M, et al. Antibody responses to SARS-CoV-2 after infection or vaccination in children and young adults with inflammatory bowel disease. *Inflamm Bowel Dis.* 2022; 28(7):1019–1026
112. Hyams JS, Dubinsky MC, Baldassano RN, et al. Infliximab is not associated with increased risk of malignancy or hemophagocytic lymphohistiocytosis in pediatric patients with inflammatory bowel disease. *Gastroenterology.* 2017;152(8):1901–1914.e3

113. Chupin A, Perduca V, Meyer A, Bellanger C, Carbonnel F, Dong C. Systematic review with meta-analysis: comparative risk of lymphoma with anti-tumour necrosis factor agents and/or thiopurines in patients with inflammatory bowel disease. *Aliment Pharmacol Ther*. 2020;52(8):1289–1297
114. Dulai PS, Thompson KD, Blunt HB, Dubinsky MC, Siegel CA. Risks of serious infection or lymphoma with anti-tumor necrosis factor therapy for pediatric inflammatory bowel disease: a systematic review. *Clin Gastroenterol Hepatol*. 2014;12(9):1443–1451, quiz e88–e89
115. Goyal A, Zheng Y, Albenberg LG, et al. Anemia in children with inflammatory bowel disease: a position paper by the IBD Committee of the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr*. 2020; 71(4):563–582
116. Werkstetter KJ, Ullrich J, Schatz SB, Prell C, Koletzko B, Koletzko S. Lean body mass, physical activity and quality of life in paediatric patients with inflammatory bowel disease and in healthy controls. *J Crohn's Colitis*. 2012;6(6): 665–673